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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/530,298	04/27/2000	Alexander Krantz	REDC-710USA	7198

7590 05/05/2004

Michael R. Ward
Morrison & Foerster LLP
425 Market Street
San Francisco, CA 94105-2482

EXAMINER	
LUKTON, DAVID	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 05/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/530,298	KRANTZ ET AL.	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1, 2, 4-35, 40-55, 58-59* is/are pending in the application.

4a) Of the above claim(s) *6-8,10-14 and 46-54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 4, 5, 9, 15-35, 40-45, 55, 58, 59* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Pursuant to a second preliminary amendment (filed 4/19/04), claim 1 has been amended. Claims 1, 2, 4-35, 40-55, 58-59 are pending. Applicants' election of Group 2 (claims 1-20, "E" is a therapeutic agent that is limited to G1) with traverse is acknowledged, as is the elected specie.

Applicants have traversed the restriction between Groups 2 and 3. The issue here is one of "extracting out" various therapeutic agents from other references. The opportunity to do this has now passed. However, the restriction between Groups 2 and 3 will not be enforced if no such "extraction" of therapeutic agents (from other documents) is undertaken by applicants. Applicants have also traversed the restriction between Groups 2 and 1. Applicants have argued lack of "serious burden". Given the Office action set forth hereinbelow, applicants should begin to acquire some insight into the potential burden on the examiner to examine claims that require "E" to be a therapeutic agent. Examining claims in which "E" is a diagnostic agent would require a greater burden still. However, in the event that claim 1 is determined to be novel based on the assumption of "E" being a therapeutic agent, the issue of rejoining claims 46-54 may be considered at that time. At the present time, however, the restriction requirement is maintained.

Claims 46-54 are withdrawn from consideration pursuant to the restriction; in addition, claims 6-8, 10-14 are withdrawn because they do not encompass the elected specie.

Claims 1, 2, 4, 5, 9, 15-35, 40-45, 55, 58, 59 are examined in this Office action.

35 U.S.C §101 reads as follows:

"Whoever invents or discovers any new and useful process, machine, manufacture or composition of matter or any new and useful improvement therof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claims 1, 2, 4, 5, 9, 15-35, 40-45, 55, 58, 59 are rejected under 35 USC §101 because the claimed invention is not supported by a well-established utility.

With respect to this ground of rejection, four categories of embodiment are now discerned:

(a) "E" is a diagnostic agent, and the claimed compound binds to albumin

(b) "E" is a therapeutic agent, and the claimed compound binds to albumin

(c) "E" is a diagnostic agent, and the claimed compound binds to a biological entity other than albumin

(d) "E" is a therapeutic agent, and the claimed compound binds to a biological entity other than albumin

This ground of rejection is directed at categories (a) and (b), not to categories (c) and (d). It is acknowledged that diagnostic agents which can be targeted to a given receptor or cell surface antigen can be quite useful. It is also acknowledged that, if the therapeutic agent can be released, a compound which binds to e.g., a cell surface antigen on a tumor cell can be useful. But to reiterate, this ground of rejection is directed at categories (a)

and (b), not to categories (c) and (d). It is not clear what the asserted utility is for compounds that bind to albumin. Absent an assertion, there can be no argument that the specification teaches the skilled artisan how to "make and use" the claimed invention. Applicants are requested to point to the page and line number where the utility of the claimed invention is asserted for the case of compounds that bind to albumin.

Claims 1, 2, 4, 5, 9, 15-35, 40-45, 55, 58, 59 are also rejected under 35 USC §112 first paragraph. Specifically, since the claimed invention is not supported by a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

✧

Claim 1 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of of U.S. Patent No. 6,602,981. Although the conflicting claims are not identical, they are not patentably distinct from each other

Claim 1 of the '981 patent encompasses the compound of example 2 (cols 9-10), which is a compound that comprises the following sequence:

YGGFLRRIRPKLK

Substituent variable "E" (instant application) could correspond to this 13-mer ; alternatively, "E" could be just the pentapeptide YGGFL, which is also an analgesic. Variable "R" can be just an amide bond, and the requirement for a "specific binding determinant" is met by the

maleimide group.

The obviousness-type double patenting rejection is a judicially established doctrine based upon public policy and is primarily intended to prevent prolongation of the patent term by prohibiting claims in a second patent not patentably distinct from claims in a first patent. In re Vogel, 164 USPQ 619 (CCPA 1970). A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) would overcome an actual or provisional rejection on this ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78(d)

✧

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4, 5, 9, 15-35, 40-45, 55, 58, 59 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Enablement for the claimed invention is lacking for those embodiments in which "E" is a therapeutic agent. In order to be able to use the claimed compounds to treat human disease, or to alter a biochemical process in a manner that would be beneficial to the host, the drug "E" must be released intact. If "E" is not released at all, it will not be effective; and if it is released with some group or moiety attached to it, it is also unlikely to be effective. When "E" is a therapeutic agent, the claimed compounds are prodrugs. If one takes a "drug" that has been shown to be effective in one way or another, and

subsequently endeavors to create a "prodrug" thereof, "unpredictable" effects *in vivo* can result. Consider the following:

- Shabat D. (*Proceedings of the National Academy of Sciences* **98** (13) 7528-33, 2001) discloses a prodrug that is not activated by endogenous enzymes. This supports the conclusion of "unpredictability" in that the instantly claimed compounds may not be activated by endogenous enzymes.

- Smal (*Biochemical Pharmacology* **49** (4) 567-74, 1995) discloses (e.g., p. 572) that 2-Leu-MTX is unsuitable as a prodrug

- Saboulard (*Molecular Pharmacology* **56** (4) 693-704, 1999) discloses (e.g., page 701, col 1) that prodrugs of AZT are not effective.

- Jaffar (*Bioorganic and Medicinal Chemistry Letters* **9** (1) 113-8, 1999) discloses (e.g., table 1) prodrugs of aspirin that are not effective.

- Deverre J. R. (*Pharmaceutica Acta Helvetiae* **67** (12) 349-52, 1992) prepared a prodrug, and discovered inactivity of the prodrug *in vivo*, either by the oral route (10 mM) or after an intraperitoneal administration (1 mM).

- Miyauchi M (*Chemical and Pharmaceutical Bulletin* **38** (7) 1906-10, 1990) discloses an attempt to produce orally bioavailable prodrugs of 3-thiazoliomethyl cephalosporin (compound number 1) Lipophilicity of the resulting derivatives (8-10) was suitable for passive absorption from the intestinal tract, and chemical stability in phosphate buffer solution (pH 6.86) was moderate. However, when administered orally to mice, these derivatives were mainly transformed to a novel 3-spiro cephalosporin 11, and desired reconversion to the 3-thiazoliomethyl cephalosporin was minor. These results showed that the derivatives (8-10) tested in this study did not serve as orally active prodrugs of 3-thiazoliomethyl cephalosporin 1.

- Hadad S (*Journal of Pharmaceutical Sciences*, **81** (10) 1047-50, 1992) examined the pharmacokinetics and efficacy of five monoester prodrugs of valproic acid (VPA). Valproic acid an anti-epileptic drug. Four of the five prodrugs were ineffective in mitigating symptoms of epilepsy. In addition, a pharmacokinetic- pharmacodynamic correlation was absent in the case of B-VPA and H-VPA.

- Langer (*J. Med. Chem.* **44**, 1341-1348, 2001) has examined the effects of bonding a peptide, via a linker, to daunorubicin and doxorubicin. As stated (p. 1344, col 1, paragraph 3, attaching a peptide to the amino group of daunorubicin or doxorubicin eliminated activity.

- Mamber S. W. (*Journal of Pharmacology and Experimental Therapeutics* **274** (2) 877-883, 1995) discloses prodrugs of taxol. The 2'- and 7- phosphate analogs BMY46366 and BMY46489 were ineffective as prodrugs.

- Niemi (*J. Med. Chem.* **42**, 5053, 1999) prepared compounds which were intended to be prodrugs of clodronic acid. As it happened, benzoyloxyproyl esters of clodronic acid were ineffective as prodrugs.

Accordingly, efficacy of prodrugs is unpredictable. In addition, the specification provides no guidance as to what points of attachment on the drug molecule (substituent variable "E") will result in an effective prodrug. There is also no guidance as to which "C_a" connecting groups will produce a prodrug that will release entity "E" intact.

Accordingly, "undue experimentation" would be required to practice the claimed invention.

Claims 33-35 and 45 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 33 recites that C_b comprises a backbone of "between about 1 and 25 atoms". However, there is a contradiction between the use of the word "between" and the use of the

word "about". Which dominates here? For example, would the number 26 be included? The number 26 is not between 1 and 25, and so, according to one interpretation, it would be excluded. On the other hand, 26 is "about" the same as the number 25, so according to this interpretation, the number 26 would be included. So the question remains, which limitation controls? A related issue concerns the meaning of "about" 1 atom. Suppose one had "zero" atoms. If a person had a vial containing "zero" atoms, would any of those zero atoms qualify as being "about" one atom? See also claims 34, 35 and 45.

✧

The following is a quotation of 35 USC §103 which forms the basis for all obviousness rejections set forth in the Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that

was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claim 1 is rejected under 35 U.S.C. §103 as being unpatentable over De Wied (USP 3,862,928) in view of Vickery (USP 6,203,820) further in view of Szekerke M. (*FEBS Letters* **44** (2) 160-3, 1974).

De Wied discloses (col 15) the following peptide:

Met-Gln-His-Phe-Lys-Trp-OMe

- De Wied does not disclose that methionine is a therapeutic agent, and does not disclose that the dipeptide methyl ester Lys-Trp-OMe exhibits affinity for albumin.
- Vickery discloses (col 4, line 1) that methionine is a therapeutic agent.
- Szekerke discloses that the dipeptide methyl ester Lys-Trp-OMe exhibits affinity for albumin.

Thus, methionine qualifies as substituent variable "E", the peptide Lys-Trp-OMe qualifies as "A", and one of the amide bonds qualifies as variable "R".

Thus, the claims are rendered obvious.

✧

Claims 1, 2-5, 9, 22, 23, 24, 30-35, 40-45 are rejected under 35 U.S.C. §103 as being unpatentable over Goodey (USP 5,302,697) in view of Vickery (USP 6,203,820).

Goodey discloses (col 1, line 1) the following peptide:

M-L-W-V-S-F-I-S-L-L-**F-L-F-S-S**-A-Y-S-R-S-L-D-K-R

Goodey does not disclose that methionine is a therapeutic agent (i.e., the N-terminal amino acid of the sequence). Vickery, however, discloses (col 4, line 1) that methionine is a therapeutic agent.

Note that the disclosed peptide contains the following pentapeptide:

F-L-F-S-S

This peptide falls within the scope of instant claim 2, when variable "R" is amide, and the amino acid variables correspond as follows:

O1 is phenylalanine

O2 is Leucine

X1 is phenylalanine

X2 is Serine

B is Serine

Claims 1 and 58 are rejected, since applicants have asserted that any peptide falling within the genus of claim 2 will exhibit affinity for serum albumin.

Claim 24 is rejected, since variable R_1 can comprise a substituted aromatic group. For example, R_1 can be ethylbenzene. If one attaches a nitrogen atom to the 2-position (of the ethyl group) of ethylbenzene, one obtains the following:

$N\text{-}CH_2\text{-}CH_2\text{-}C_6H_5$

If one then attaches a carbonyl group to the carbon bearing nitrogen, the result is phenylalanine.

Thus, the claims are rendered obvious.

✧

Claims 1 and 58 are rejected under 35 U.S.C. §103 as being unpatentable over Hsia (USP 5,741,893).

Hsia discloses (col 36, line 48+) nitroxide-labeled albumin for a variety of diagnostic and therapeutic purposes. Clearly, the disclosed compound contains a moiety corresponding to "E" of instant claim 1. In the preferred embodiment of instant claim 1, variable "A" has affinity for albumin. In reality, albumin itself has affinity for (other molecules of) albumin. This is implied by the reference at col 37, line 18+ and col 24, line 63+. Thus, the diagnostic and therapeutic compounds of Hsia have affinity for albumin.

Thus, the claims are rendered obvious.

✧

Claims 1 and 58 are rejected under 35 U.S.C. §103 as being unpatentable over Robson (USP 5897863) in view of Chang (USP 5,250,662).

Robson discloses (col 5, line 1) conjugation of a therapeutic agent to albumin. Robson does not disclose that albumin has affinity for other molecules of albumin. Chang discloses (col 11,line 37) that albumin forms aggregates, thus implying that albumin has affinity for other molecules of albumin.

In the preferred embodiment of instant claim 1, variable "A" has affinity for albumin. Thus, a conjugate of albumin with a therapeutic agent meets the requirements of instant claims 1 and 58. The claims are rendered obvious.

✧

Claim 1 is rejected under 35 U.S.C. §103 as being unpatentable over are rejected under 35 U.S.C. '103 as being unpatentable over Greenfield (U.S.P. 4,933,288) or Woo (U.S.P. 5,130,116) or Ferris (USP 4,808,705) or Sivam (USP 4,981,979).

Each of the cited references discloses immunoconjugates of therapeutic or diagnostic agents. As it happens, almost any immunoconjugate would anticipate claim 1, or render it obvious. Clearly the antibody possesses "specific binding determininants for a target molecule". In addition, any immunoconjugate will contain amide bonds, thus meeting the requirement for (instant variable) "R".

Thus, the claim is rendered obvious.

✧

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at 571-272-0951. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.